American Journal of Medical Genetics 64:323–328 (1996)

Neuropsychological Profiles of Three Sisters Homozygous for the Fragile X Premutation

Michèle M.M. Mazzocco and Jeanette J.A. Holden

Behavioral Neurogenetics and Neuroimaging Research Center, Kennedy Krieger Institute, and Department of Psychiatry, The Johns Hopkins School of Medicine, Baltimore, Maryland (M.M.M.M.); Department of Psychiatry, Queen's University and Ongwanada Resource Centre, Kingston, Ontario, Canada (J.J.A.H.)

Fragile X syndrome (fraX) is associated with an amplification of a CGG repeat within the fraX mental retardation (FMR-1) gene. We describe an exceptional family in which 3 adult sisters are homozygous for the FMR-1 premutation. Each sister inherited 2 premutation alleles (ca. 80 CGG repeats) from their biologically unrelated parents. The 3 sisters were administered measures of executive function, visual spatial, memory, and verbal skills. Deficiencies in the first 2 of these domains have been reported among females with the full mutation. The sisters' performances were compared with available normative data and with published group means for females affected by fraX. These women did not appear to have verbal or memory difficulties. None of the women demonstrated a global executive function deficit, and none had global deficits in spatial ability. The profiles of these sisters are consistent with reports that the fragile X premutation does not affect cognitive performance.

KEY WORDS: fragile X, homozygous, premutation, neuropsychological profile

INTRODUCTION

The fragile X syndrome (fraX) is associated with an expansion of a cytosine-guanine-guanine (CGG) repeat within the fraX mental retardation (FMR-1) gene. The discovery of this expansion in 1991 [Verkerk et al., 1991] led to the identification of an apparent threshold (ca. 200 CGG repeats) differentiating the full mutation (fM), which has been associated with significant developmental delays, from the premutation (pM). Carriers of the pM have a CGG amplification that exceeds the reported modal (29) or high end of normal (52) [Fu et al., 1991] number of CGG repeats. Over the last several years, findings across different studies have been inconsistent with respect to cognitive effects of the pM [Mazzocco et al., 1993; Reiss et al., 1993; Dorn et al., 1994; Loesch et al., 1994; Rousseau et al., 1994; Taylor et al., 1994; Feng et al., 1995]. Despite case reports to the contrary, the majority of these studies are indicative of a lack of an effect of the pM on psychopathology or cognitive performance [Mazzocco et al., 1993; Reiss et al., 1993; Feng et al., 1995]. In this paper, cognitive skills among 3 sisters homozygous for the fragile X pM are examined.

In females, the study of potential pM effects is confounded by the presence of an X chromosome that does not contain the fragile X mutation. Therefore, a lack of cognitive effects of the pM among females may result directly from a lack of effects associated with the pM or from countereffects of the additional non–fragile X chromosome. Support for either the no-effects or the countereffects hypotheses would have important clinical implications. Although direct evidence regarding pM effects (or lack thereof) on males can be gathered through studies of pM males, the only instance among females for which no normal FMR-1 gene is present would be instances in which both X chromosomes have a pM or fM. Only 1 family in which the latter is demonstrated has been identified (Holden et al., in preparation).

The present report includes information from a rare family in which all 3 adult sisters are homozygous for FMR-1 mutations. Each sister inherited pM alleles (ca. 80 CGG repeats) from their biologically unrelated parents. The aim of this report is to examine whether the sisters manifest a neuropsychological phenotype that is similar to that reported for women affected by fragile X. It is not necessarily the case that the pM effects will be of similar magnitude as those reported for affected women. Regardless of the degree of involvement, it is important to identify whether effects of the pM are seen in females for whom no normal FMR-1 gene is present.

Received for publication August 23, 1995; revision received December 14, 1995.

Address reprint requests to Jeanette Holden, Ongwanada Resource Centre, 191 Portsmouth Avenue, Kingston, Ontario K7M 8A6 Canada.

Toward this objective, a neuropsychological battery was designed to include tasks for which difficulties for women affected by fraX have been reported or items representing domains that have been investigated in affected females with fraX. These neuropsychological domains include executive function, visual spatial, memory, and verbal skills [e.g., Miezejeski et al., 1986; Grigsby and Myers, 1987; Grigsby et al., 1990; Freund and Reiss, 1991, 1996; Mazzocco et al., 1993; Kovar et al., *1996]. Ideally*, a comparison would have been made between these sisters and age- and sex-matched non–fragile X relatives, but such relatives were not available. Not all neuropsychological measures used in this study have been well standardized, and thus it was not possible merely to report the range of scores obtained by these sisters. Therefore, the performance of these sisters was examined with respect to available normative data and to profiles reported for women affected by fraX. If the pM does affect neuropsychological performance, these sisters should demonstrate deficits comparable in quality, although not necessarily in magnitude, to deficits seen in each other and to deficits manifested by women affected by the fraX fM.

MATERIALS AND METHODS

Subjects

The subjects were 3 adult sisters close in age (34, 33, and 32 years old at time of testing; hereafter referred to as S1, S2, and S3, respectively) without other sibs. The propositus in the family was an affected son with an fM, who has 2 pM brothers. Two of the sisters each have 1 child, in each case a daughter with a pM. In S1, the 2 pM alleles are approximately 77 and 88 repeats. S2 has alleles close to 78 and 108 repeats; and S3 has 2 alleles, each with 80–82 repeats. For each woman, transmission of the FMR-1 mutations to offspring was accompanied by an increase in the number of CGG repeats [for a more detailed description of the molecular genetic characteristics in this family (see Holden et al., in preparation) (see Fig. 1).

Materials

Overall intellectual functioning measure. The Wechsler Adult Intelligence Scale–Revised [WAIS-R; Wechsler, 1981] was administered to each woman. Three standard scores obtained from the WAIS-R included the Full Scale IQ (FSIQ), Verbal IQ, and Performance IQ scores.

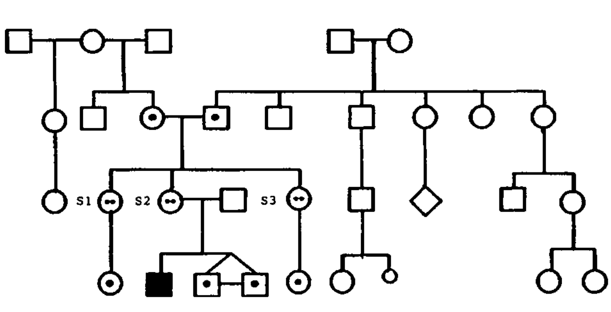

Fig. 1. Pedigree. ■, affected male; ⊡, premutation carriers; ⊙, individuals with two premutations.

Verbal measures. The 2 verbal measures included an oral nonword reading task [Olson et al., 1994] to measure phoneme awareness and a verbal short-term (story) memory (STM) task from the Wechsler Memory Scale–Revised [WMS-R; Wechsler, 1987]. The number of correctly read nonwords is recorded for the former; an age-percentile score is obtained for the latter.

Executive function measures. Four measures of executive function were administered. The Contingency Naming Test [Taylor, 1988] was used as a measure of impulse control and mental flexibility [for a detailed description of this test, see Mazzocco et al., 1992]. The time needed to complete the naming task and the response time needed to complete the task are recorded. The Wisconsin Card Sorting Task [WCST; Heaton, 1981], Trails B [Reitan and Wolfson, 1985], and the Stroop [Golden, 1978] tests were used to measure varying degrees of ability to maintain and shift mental set. During administration of the WCST, the participant sorts cards according to category-based rules that must be inferred from the examiner's feedback to the participant's sorting behavior. The number of category-based rules achieved and the number of perseverations to an earlier category-based rule are recorded. For the Trails B test, the participant is simply asked to draw a line (in a "connect the dots" manner) between alternate numbers and letters in order (i.e., connect 1 to a to 2 to b, etc.). For the Stroop test, the participant is required to name the color of ink in which a series of color names is presented. That is, the word "red" printed in blue ink must be identified as "blue." Each task is used to measure a component of executive function.

Visual–spatial measures. Five visual–spatial measures were employed. The Spatial Relations subtest from the Woodcock Johnson Tests of Cognitive Ability [Woodcock and Mather, 1989] is a measure in which the participant must choose, from an array of 6 or more designs, those designs that comprise a puzzle depicted next to the array. The number of correct responses is recorded. The design STM measure from the WMS-R was also employed, from which an age-percentile score was obtained. The Shepard Metzler Mental Rotations task was administered as a 3-dimensional mental rotations task [Shepard and Metzler, 1971]; an age-percentile score based on the number of correct responses was obtained. The Judgment of Line Orientation (JLO) test [Benton et al., 1983] was administered to assess the participant's ability to correctly select 2 lines from an array of 11 choices that are presented at the same angle as a pair of target lines. The Rey-Osterrieth Complex Figure Drawing test [Rey, 1941; Osterrieth, 1944] was used to measure the participants' ability to reproduce and recall a complex design. An inventory score was obtained from this measure, based on the number of features reproduced when copying the design or when reproducing the design from memory. Age-percentile scores were based on age-specific normative data reported in Kolb and Wishaw [1985].

Long-term memory. The long-term memory (LTM) items included delayed requests for the verbal (story) and design STM stimuli, which occurred approximately 30 min after the corresponding STM task.

Procedure

All 3 sisters were tested individually in their respective domiciles by the same female examiner (M.M.M.M.). The testing occurred on 2 separate occasions, approximately 4 months apart, with each session lasting approximately $2^1/_2$ hr. Each woman received the same group of tests on each of the 2 testing sessions. Performance by the 3 sisters was compared with available norms or published group data.

RESULTS

A formal statistical analysis of the women's performance was not appropriate. Their individual test scores (as seen in Tables I–IV), when possible, were compared with normative data or with data from women affected by fragile X. The scores are discussed within the domain with which they are most frequently associated.

WAIS-R Performance

The women's FSIQ scores were within the Below Average to Average range. Specifically, these FSIQ scores are at the 34th, 32nd, and 8th percentile, for S1, S2, and S3, respectively. There was no consistent pattern of overall subtest profiles from the WAIS-R seen across the 3 subjects. For instance, a wide range of scaled scores was seen on the Block Design (BD) subtest: S3's BD scaled score was consistent with her overall narrow range of scores (scaled score = 7; other scaled scores ranged from 5 to 8); S2's BD score was lower than the majority of her other scaled scores (scaled score = 7; remaining scores include a 4 and scores from 8 to 13); and S1's BD score was among her highest scaled score (scaled score = 11; remaining scaled scores ranged from 7 to 12). Only S2 had remarkable difficulty on the Object Assembly subtest (scaled score = 4; her next lowest scale score was 7). S1 and S3 received scores of 9 and 8 on this subtest, respectively.

The findings do show some degree of difference in FSIQ between S3 and her sisters. Thus, when available, age-percentile scores were used to evaluate each woman's performance, relative to her FSIQ score, on measures discussed below.

Verbal Performance Scores

Each woman received a high score on a test of nonword reading, indicating a lack of difficulty with phoneme awareness. The age-percentile scores obtained on the WMS-R verbal (story) STM, relative to performance on the WAIS-R, did not demonstrate a deficit. Indeed, for S1 and S3, the verbal STM score was higher than each woman's age-percentile score on the WAIS-R. Thus, none of the sisters displayed deficits on these 2 measures of verbal performance (see Table II).

TABLE I. IQ Scores for Each Sister

WAIS-R variable	Sisters S3	S2	S1
FSIQ	79	93	94
VIQ	79	94	96
PIQ	82	93	92

TABLE II. Scores for Each Sister on Measures of Memory and Nonword Reading

Variable	Sisters S3	S2	S1
WMS-R age percentile:			
Verbal STM	81	35	55
Design STM	24	65	74
Verbal LTM	75	58	67
Design LTM	30	69	44
Nonword reading:			
No. correct/84	77	81	81

Executive Function Scores

Four measures of executive function skills were administered to each woman. Many executive function measures were included in part because of the range of skills attributed to this domain (e.g., goal-oriented tasks including impulse control, mental flexibility, and strategic planning) and because of the reported evidence for deficits in this area among females affected by fraX [e.g., Grigsby et al., 1987; Mazzocco et al., 1993; Freund and Reiss, 1996]. Females with fraX have been reported to make more perseverative errors and to achieve fewer categories on the WCST [e.g., Mazzocco et al., 1993; Freund and Reiss, 1996], have longer response times and make more errors on the CNT [Mazzocco et al., 1992; Kovar et al., 1996], and have longer response times on the Trails B test [Freund and Reiss, 1996] relative to controls and/or obligate carriers. These 3 measures were administered to the sisters in addition to the Stroop test.

Scores obtained on these tests are presented in Table III. Performance among the women was variable for the WCST; only S2 demonstrated a lack of remarkable difficulty. On the CNT, only S3 had notable difficulty with all 3 components of the test: response time, trials

TABLE III. Scores for Each Sister on Measures of Executive Function

Variable	Sisters S3	S2	S1
WCST:			
No. of categories/6	3	6	6
No. of perseverative errors	16	14	26
CNT-B:			
Response time (sec)	157	97	135
Trials to criteria	8	3	4
Errors + self corrections	23	4	5
Stroop test, T score:			
Word	39	71	44
Color	42	53	45
Interference	48	56	45
Trails B:			
Response time (sec)	24	18	28
No. of errors	0	0	0

TABLE IV. Scores for Each Sister on Measures of Visual-Spatial Skills

Variable	Sisters S3	S2	S1
JLO:			
No. correct/30	14	28	24
Rey-Osterrieth			
Inventory score/36:			
Copy	24	33	34
Delayed recall	14.5	12	15
WJ cognitive			
Spatial relations:			
Raw score/33	15	17	20
Age percentile	4	10	14
Mental rotations:			
Age percentile	54	19	54

needed to learn the rule, and number of errors made. Although neither S1 nor S2 had dramatic difficulty with the CNT, they did make some errors and did require 1 or 2 (respectively) additional trials to learn the most difficult "set-shifting" rule of the test. Nevertheless, these levels of performance certainly fall within the range reported for unaffected and control women [Mazzocco et al., 1993]. Finally, the sisters had average or above average scores on the Stroop and Trails B tests. Although each sister demonstrated some difficulty on at least one of the executive function measures, none had difficulty on all 4 measures; nor did any 1 of the 4 tests discriminate ability level across the sisters. Deficiency in executive function was not a global finding in any one sister, contrary to reports of specific executive function deficits in females affected by fraX [Mazzocco et al., 1992, 1993].

Long-Term Memory Performance

Across the 3 women, age-percentile scores for both verbal and figural LTM were at least as strong as their individual age-percentile scores for their FSIQ scores.

Visual-Spatial Performance

Each of the 5 visual–spatial measures employed is a measure for which data on females with fraX have been reported. Performance on 4 of these measures was variable across the 3 women, as seen in Table IV. Only S3 had remarkable difficulty on the JLO and on the Mental Rotations task. All 3 women appeared to have some difficulty on the Rey-Osterrieth test. The women's age-percentile scores on the figural STM task from the WMS-R were variable. Although S3's figural STM score was lower than those of her sisters, this result is consistent with her generally lower performance on other measures, including the WAIS-R. On the WJ-R spatial relations subtest, each woman received an age-percentile score that was lower than her age-percentile scores for all other tests included in this study (for which age-percentiles are available). In summary, deficiency in the visual–spatial domain was not global among these women, but difficulty with the Rey-Osterrieth and the spatial relations subtest was seen consistently among all three.

DISCUSSION

No global within-domain deficits were seen among these homozygous sisters. There was no striking similarity among each other's performance, nor between the performance of these women and that reported for women affected by fraX. The primary inconsistency between these women and reports of affected women is the lack of overall executive function deficits. The findings that are consistent with earlier reports of affected women include the relative strength in verbal memory (and in LTM per se), but these strengths alone are hardly indicative of effects of fraX.

It was not possible to derive evidence of effects (or lack thereof) from the women's FSIQ scores alone because the ranges reported for both affected and unaffected women include these scores [Pennington et al., 1991; Mazzocco et al., 1993] and because information regarding other potential contributing factors (such as midparental FSIQ) were not available. The subtest patterns do not reveal a consistent pattern of strengths or weaknesses across the women.

With respect to verbal skills, each woman's nonword reading performance indicated a lack of difficulty with phoneme awareness, and each woman's verbal STM score was consistent with her performance on the WAIS-R. Thus, none of the sisters displayed deficits on the 2 measures of verbal performance. Although the particular strength in S3's verbal LTM versus her remarkable difficulty in executive function and her lower FSIQ was similar to profiles reported for fraX-affected women and girls [Mazzocco et al., 1993; Freund and Reiss, 1996; Kovar et al., 1996]; the absence of this profile among S1 and S2 prohibits the attribution of S3's profile to pM effects or at least to pM effects alone.

The sisters' difficulty on the WJ-R spatial relations test was the most consistent within-group finding. The WJ-R spatial relations is a test on which deficits among affected fraX women [Mazzocco et al., 1993] and girls [Kovar et al., 1996] have been reported. Although this finding is also consistent with reports of visual–spatial deficits associated with fraX, it occurred in the absence of evidence for global visual–spatial deficits. It is important to consider, in light of the role of mental rotation required for successful performance on this test, the considerable evidence for gender-specific difficulty for mental rotation tasks and spatial ability in general among females [Birenbaum et al., 1994].

Identification of factors that may contribute to difficulty with the spatial relations subtest would guide additional studies of the specific deficiencies potentially associated with the pM. In the spatial relations subtest, the subject is asked to identify which pieces from an array of up to 8 items fit into a reconstructed whole that is depicted to the left of the array. Many factors may contribute to success on this task, and many of these factors can be ruled out as sources of difficulty for the women in this study. Successful performance on the spatial relations test is not dependent on memory because the items included in the spatial relations task are static and present throughout each problem. Some degree of mental rotation ability is necessary to solve some spatial relations problems successfully, yet the

women's performance on the mental rotations test suggests that this is not a contributing factor to the women's difficulty. Lack of impulse control would interfere with successful performance on spatial relations, yet this factor would also interfere with success on the mental rotations and JLO tests and therefore cannot be implicated as a contributor to the sisters' difficulty given their adequate or better performance on these 2 tasks. Recognition of subtle changes in angle are not required to solve spatial relations problems nor does this skill appear to be a problem for 2 of the sisters, as supported by the JLO performance. Thus, memory limitations, inability to mentally rotate items, poor impulse control, and difficulty differentiating degrees of angles do not appear to explain these subjects' difficulty on the spatial relations subtest.

Detection of subtle differences in shape and size are necessary for successful completion of the spatial relations subtest (and not for success on mental rotations or on the JLO), as is some degree of recognizing components of a "whole" item comprised of "pieces." The variability (across the 3 sisters) of performance in block design and object assembly suggests that, although each woman has some difficulty in visual–spatial skills, their visual spatial difficulties are manifested differently. Despite these differences, it is possible that these spatial difficulties are related to each other and to the women's performance on the spatial relations subtest.

As is true for all case studies, we cannot draw conclusions regarding the effects of the pM from such limited data. Information obtained from this family is limited to pM in the ranges seen among the 3 women whose performances we have examined, and the current report is based on cognitive data alone. An additional limitation of the present study is the biological relationship among these women. For instance, genes other than the FMR-1 pM may be contributing to the spatial difficulty. Although based on these women alone, the evidence from this report clearly shows that (1) these women did not display deficits of the magnitude associated with affected women carriers of FraX, (2) the sisters did not appear to have verbal or memory difficulties, (3) none of the women demonstrated a global executive function deficit, and (4) none of the women showed global deficits in spatial ability. Considered together, the profiles of these 3 sisters are consistent with reports that the fragile X pM does not affect cognitive performance.

ACKNOWLEDGMENTS

This study was supported by grants from the Ontario Mental Health Foundation (OMHF-1005-88-92) and the Medical Research Council of Canada (MRC MT-10862 to J.J.A.H.). J.J.A.H. was the recipient of an Ontario Mental Health Foundation Travel Fellowship (1991–1992). M.M.M.M. received additional support from grant MH50047-01 from the National Institutes of Health. The support, interest, and dedication of the 3 sisters is greatly appreciated.

REFERENCES

Benton AL, Hamsher KS, Varney N, Spreen O (1983): "Contributions to Neuropsychological Assessment." New York: Oxford University Press.

Birenbaum M, Kelly A, Levi-Keren M (1994): Stimulus features and sex differences in mental rotation test performance. Intelligence 19:51–64.

Dorn MB, Mazzocco MM, Hagerman RJ (1994): Behavioral and psychiatric disorders in adult male carriers of fragile X. J Am Acad Child Adolesc Psychiat 33:256–264.

Feng Y, Lakkis L, Devys D, Warren, ST (1995): Quantitative comparison of FMR1 gene expression in normal and premutation alleles. Am J Hum Genet 56:106–113.

Freund LS, Reiss AL (1991): Cognitive profiles associated with the fra(X) syndrome in males and females. Am J Med Genet 38: 542–547.

Freund LS, Reiss AL (1996): A neurocognitive phenotype of young males and females with fragile X. Dev Neuropsychol (in press).

Fu YH, Kuhl DPA, Pizzuti A, Pieretti M, Sutcliffe JS, Richards S, Verkerk AJMH, Holden JJA, Fenwick Jr RG, Warren ST, Oostra BA, Nelson DL, Caskey CT (1991): Variation of the CGG repeat at the fragile X site results in genetic instability: Resolution of the Sherman paradox. Cell 67:1047–1058.

Golden C (1978): "Stroop Color and Word Test." Wood Dale, IL: Stoelting Company.

Grigsby JP, Myers CS (1987): Neuropsychological findings among heterozygous fragile X females. Paper presented at the First National Fragile X Conference, Denver, CO, December 1987.

Grigsby JP, Kemper MB, Hagerman RJ (1987): Developmental Gerstmann syndrome without aphasia in the fra X syndrome. Neuropsychologia 25:881–891.

Grigsby JP, Kemper MB, Hagerman RJ, Myers CS (1990): Neuropsychological dysfunction among affected heterozygous fragile X females. Am J Med Genet 35:28–35.

Heaton R (1981): "Wisconsin Card Sorting Test Manual." Odessa, FL: Psychological Corporation.

Kolb B, Whishaw I (1985): "Fundamentals of Human Neuropsychology." New York: Freeman and Co.

Loesch DZ, Hay DA, Mulley J (1994): Transmitting males and carrier females in fragile X-Revisited. Am J Med Genet 51:392–399.

Mazzocco MM, Hagerman RJ, Pennington B (1992): Problem-solving limitations among cytogenetically expressing fragile X women. Am J Med Genet 43:78–86.

Mazzocco MM, Pennington BF, Hagerman RJ (1993): The neurocognitive phenotype of female carriers of fragile X: Additional evidence for specificity. J Dev Behav Pediatr 14:328–335.

Miezejeski CM, Jenkins EC, Hill AL, Wisniewski K, French JH, Brown WT (1986): A profile of cognitive deficit in females from fragile X families. Neuropsychologia 24:405–409.

Olson R, Forsberg H, Wise B, Rack J (1994): Measurement of word recognition, orthographic, and phonological skills. In Lyon GR (ed): "Frames of Reference for the Assessment of Learning Disabilities." Baltimore, MD: Paul H. Brookes, pp 243–277.

Osterrieth PA (1944) Le test de coupe d'une figure complex. Archiv Psychol 30:206–356.

Pennington BF, Schreiner RA, Sudhalter V (1991): Towards a neuropsychology of fragile X syndrome. In Hagerman S (ed): "The Fragile X Syndrome." Baltimore, MD: Johns Hopkins University Press, pp 173–201.

Reiss AL, Freund L, Abrams MT, Boehm C, Kazazian H. (1993): Neurobehavioral effects of the fragile X premutation in adult women: A controlled study. Am J Hum Genet 52:884–894.

Reitan R, Wolfson D (1985): "The Halstead Reitan Neuropsychological Test Battery." Tucson, AZ: Neuropsychology Press.

Rey A (1941) L'examen psychologique dans le cas d'encephalopathic traumatique. Archiv Psychol 28:286–340.

Rousseau F, Heitz D, Tarleton J, MacPherson J, Malmgren H, Dahl N, Barnicoat A, Mathew C, Mornet E, Tejada I, Maddalena A, Spiegel R, Schinzel A, Marcos JAG, Schwartz C, Mandel JL (1994): A multicenter study on genotype-phenotype correlations in the fragile X syndrome, using direct diagnosis with probe StB12.3: The first 2,253 cases. Am J Hum Genet 55:225–237.

Shepard R, Metzler J (1971): Mental rotation of three-dimensional objects. Science 171:701–703.

Taylor AK, Safanda JF, Fall MZ, Quince C, Lang KA, Hull CE, Carpenter I, Staley LW, Hagerman RJ (1994): Molecular predictors of cogni-

tive involvement in female carriers of fragile X syndrome. JAMA 271:507–514.

Taylor H (1988): Learning disabilities. In Mash E (ed): "Behavioral Assessments of Childhood Disorders, 2nd edition." New York: Guilford Press, pp 402–405.

Verkerk AJ, Pieretti M, Sutcliffe JS, Fu YH, Kuhl DP, Pizzuti A, Reiner O, Richards S, Victoria MF, Fuping Zhang MFV, Eussen BE, van Ommen GJB, Blonden LAJ, Riggins GJ, Chastain Jl, Kunst CB, Galjaard H, Caskey CT, Nelson DL, Oostra BA, Warren ST (1991): Identification of a gene (FMR-1) containing a CGG repeat coincident with a breakpoint cluster region exhibiting length variation in fragile X syndrome. Cell 65:905–914.

Wechsler D (1981) "Manual for the Wechsler Adult Intelligence Scale—Revised." San Antonio, TX: Psychological Corporation.

Wechsler D (1987): "The Wechsler Memory Scale—Revised." San Diego: Psychological Corporation.

Woodcock R, Mather N (1989) "Manual for the Woodcock-Johnson Tests of Cognitive Ability." Allen, TX: DLM Teaching Resources.